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Editorial
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CAR-T and Lymphomas: Long-Term Follow-Up and Real-World Evidence Confirms Therapeutic Revolution

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Editorial

Chimeric antigen receptor T-cell therapy has become part of the treatment landscape in aggressive lymphomas [1,2]. The exciting results of clinical studies often have some areas for improvement, such as inadequate follow-up length, particularly in phase II studies [3]. Favorable early effects on Progression-Free Survival (PFS) may not be maintained in the longer term and may not lead to reductions in disease-related mortality [4]. Clinically essential findings can arise several years after treatment is completed and an early analysis can give a distorted view of a treatment's outcomes. In the last few months of this year, updates of several CAR-T studies were presented at major international meetings, and the results that have come out confirm that we are facing an epochal revolution.

The final analysis of the ALYCANTE phase II clinical trial (NCT04531046) [5-7], focusing on the use of Axicabtagene Ciloleucel (Axi-Cel) in patients with Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL) after a previous line of therapy and unable to undergo Autologous Stem Cell Transplantation (ASCT), was presented at the 2023 EHA Congress. The primary outcome was Complete Metabolic Response (CMR) 3 months after CAR-T infusion. The study met its primary endpoint, with a CMR of 71% (n=44/62) at three months compared with 12% with standard of care, while 75.8% of patients achieved an objective response at three months. At six months, 59.7% of patients remained in CMR. The best Overall Response Rate (ORR) and Complete Response (CR) were 91.9% and 82.3%, respectively. Median PFS from infusion was 11.8 months, and PFS at 12 months was 48.8%. Median Overall Survival (OS) was not achieved, and OS at 12 months was 78.3%. Axi-Cel showed an acceptable safety profile in this population, which was considered unsuitable for ASCT. In 62 patients included in the ALYCANTE trial, Circulating Tumor (CT) DNA was monitored before and after infusion of the CAR-T. The results suggested that early clearance of CT DNA at day 14 and month one post-infusion predicted the outcome after Axi-Cel infusion. The ALYCANTE trial was the first study to evaluate CAR-T as second-line therapy for patients with R/R DLBCL not eligible for ASCT. Results showed high response rates and durable remission in these difficult-to-treat patients.

EHA 2023 was also the venue for the presentation of the results of two real-world studies supporting, respectively, the use of Axi-Cel against RR Follicular Lymphoma (FL) [8] and brexucabtagene autoleucel (Brex-Cel) in mantle cell lymphoma (MCL) [9].

Real-world analysis of patients with RR FL treated with Axi-Cel showed that ORR and complete CR rates were 93% and 84%, respectively, and were similar to data from the ZUMA-5 clinical trial [10]. PFS and OS at six months were 88% and 96%, respectively, and were comparable regardless of ZUMA-5 eligibility. Patients had a median of 4 prior lines of therapy (14% who had also undergone previous ASCT). These findings support the continued broad use of Axi-Cel to treat R/R FL.

Prospective data from 380 patients with RR MCL [9] showed a 90% ORR, similar to the results of the ZUMA-2 trial [11], and a high CR (78%) in patients who had received CAR-T. In addition, at 12 months, the Duration of Response (DoR), PFS, and OS rates were 64%, 61%, and 74%, respectively. These findings suggest that real-world outcomes with Brexu-Cel are consistent regardless of prior BTKi, Bendamustine, or AUTO-SCT. Moreover, Brexu-Cel in earlier lines may help achieve a higher CR rate.

A three-year follow-up of Brexu-Cel in the ZUMA-2 study showed that ORR among all 68

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treated patients was 91% with 68% CR [12]. Medians for DoR, PFS, and OS were 28.2 months, 25.8 months, and 46.6 months, respectively. These data, representing the most extended follow-up of CAR T-cell therapy in patients with MCL, suggest that CAR-T induced durable long-term responses with manageable safety.

The ZUMA-7 trial showed a significant improvement in efficacy with Axi-Cel therapy compared to second-line SoC in patients with RR DLBCL [13]. Axi-Cel was the first treatment in nearly 30 years to demonstrate a significant improvement in survival in this population. The most recent data updates from ZUMA-7 were presented orally at the American Society of Clinical Oncology (ASCO) annual meeting and published soon afterward [14]. The primary endpoint of the study was EFS. Axi-Cel demonstrated a 2.5-fold increase in primary EFS in patients who were alive after two years and had not experienced progression or required additional treatment (40.5% *vs.* 16.3%), as well as a four-fold increase in median primary EFS (8.3 *vs.* 2.0 months) compared with SoC. Nearly three times as many patients randomized to Axi-Cel eventually received definitive CAR-T treatment (94%), and compared with those treated as per standard protocol, it was observed that more patients responded to Axi-Cel (objective response rate: 83% *vs.* 50%) and achieved a CR (65% *vs.* 32%). At a median follow-up of 4 years, the treatment with Axi-Cel demonstrated significantly longer OS compared with SoC, with a 27.4% reduction in the risk of death, corresponding to a 38% relative improvement in OS in patients with DLBCL RR within 12 months of completing first-line therapy. The primary analysis was conducted as per protocol five years after randomization of the first patient-demonstrated superior OS with Axi-Cel compared with the control arm.

Regarding OS, the benefit of Axi-Cel over standard treatment was also similar in major patient subgroups, including those with high-risk features (refractory primary disease, high-grade B-cell lymphoma, double-hit lymphomas, and age 65 years or older). PFS confirmed the benefit of Axi-Cel, with 48-month estimates of 41.8% with CAR-T compared with 24.4% with SoC. Axi-Cel is the only treatment to demonstrate a statistically significant improvement over SoC second-line treatment in DLBCL. At a median follow-up of 47.2 months, ZUMA-7 showed a 27% reduction in the risk of death compared with SoC. At four years, 54.6% of patients who received CAR-T were alive compared with 46% in the comparison arm. Notably, within this arm, 57% received third-line cell therapy.

These are unprecedented data in the last 30 years in treating aggressive lymphomas, which is excellent news for the scientific community and, most importantly, patients. However, not all patients can be candidates for CAR-T therapy, and not all treatments are thriving: The selection of cases to be treated, considering the risk/benefit ratio for each, is essential for them to be prescribed appropriately. The challenge is to optimize CAR-T therapy by performing it on the patient who can benefit the most, offering a chance of definitive healing.

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